Thallium

A Review and Summary of Medical Literature

By

FRANCIS F. HEYROTH, M.D.

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G. ST. J. PERROTT, *Chief of Division*

This manuscript was prepared during the war at the request of the Committee on Insect and Rodent control of the Office of Scientific Research and Development. Thallium is used as a rodenticide. Information on its toxicity and potential dangers, including methods of treatment, were absolutely necessary for its use for general rodenticide purposes. This manuscript was used by the Army, the Navy, and the United States Public Health Service during the war. Since the end of the war, several cases of thallium poisoning with deaths have occurred from the use of thallium as a rodenticide. Requests from official agencies, such as State Health Departments, and private practitioners, for the information in this manuscript have been received repeatedly during the past year.

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THALLIUM
A REVIEW AND SUMMARY OF MEDICAL LITERATURE

FRANCIS F. HEYROTH, M.D.

From the Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati

HISTORY

In 1861, in the course of the spectroscopic examination of deposits on the flues from an oven in which sulfur-containing ores had been roasted, Crookes *(70)* observed a previously-unknown green line (535.0 m mu) which he attributed to a new element. Because the color of the line suggested that of young vegetation, he gave the element the name "thallium" from a Greek word *thallus* for a budding twig. During the following year, its chemical properties were investigated by Crookes *(71, 72, 73, 74)*, and by Lamy (*160, 161, 162*), who found it in the sludge in the lead chambers of a Belgian factory producing sulfuric acid. During the course of his work, Lamy (*160*) experienced weakness and felt pain in his legs, symptoms which led him to test the toxicity of the sulfate of the new element by feeding it to dogs, ducks and hens. All died within a few days, after having given evidence of intestinal and respiratory embarrassment, peripheral paralyses and general weakness (*161*). Although Crookes (*74*) doubted the toxicity of thallium and is said to have taken several grains of a thallium compound without suffering ill effects, both Paulet (*211*) and Grandeau (*124, 125*), after further experimentation, expressed the opinion that it is more toxic than lead.

SOURCE, PROPERTIES AND USES

Although thallium occurs in small amounts in minerals such as crookesite, lorandite, hutchinsonite and urbaite, its chief source is pyrites, in which it occurs as an impurity (*190*). During the roasting of the ore for the production of sulfur dioxide, it passes into the dust which settles on the flues or accumulates in the sludge in the lead chambers. After extraction from the dust or sludge by means of dilute sulfuric acid, the element is precipitated as the relatively insoluble chloride by the addition of concentrated hydrochloric acid. After conversion into the soluble sulfate, the element may be liberated by electrolysis or by the action of zinc. Smaller quantities of thallium compounds are obtained by similar methods from zinc sulfate prepared from zinc-bearing pyrites which contain thallium as an impurity.

In appearance, thallium resembles tin, but is soft and malleable like lead. It melts at about 300°C., and boils at about 1482°C. (*158*). It forms

univalent thallous salts and trivalent thallic salts; the latter are more or less readily hydrolyzable by water and on boiling tend to be reduced to thallous compounds. Thallous acetate, a light yellow to white powder, is soluble in cold water, but thallous chloride, thallous iodide and thallous hydroxide are insoluble.

Compounds of thallium have been used to impart a high refractive index to glass intended for lenses and for imitations of precious stones. They are of some use in pyrotechnics, in the preparation of catalysts, in the analytical laboratory, and in extending the life of the tungsten filaments of lamps. The metal has been added to the mercury employed in thermometers intended for use at low temperatures.

Thallium sulfate was found effective as a rodenticide in Germany about 1920 (*138*), and was marketed in the form of Zelio paste and Zelio granules, preparations which contained it to the extent of about 2 percent. Investigations by the Division of Predatory Animal and Rodent Control, United States Bureau of Biological Survey (*201*) confirmed its effectiveness in the eradication of rats. It has been used in the control of prairie dogs and ground squirrels that had resisted strychnine baits. In California "Thallgrain," prepared to contain 1 percent of thallium sulfate, was at one time distributed over certain areas of 10 counties in a program for the control of ground squirrels (*153*). Pastes and syrups containing thallium also have been used for the eradication of certain species of ants in the Southwest (*215*).

DETECTION AND DETERMINATION

Thallium can be detected readily by means of the spectroscope. Methods for its determination in biological material have been reviewed by Gettler and Weiss *(111)*. Among the earlier methods were those of Bodnár and Terényi *(18)*, Schee *(239)*, Stich *(255)* and Schwarzacher *(244)*. Although various precipitants, as mercaptobenzothiazole (*252*) and dithizone (*9*) have been suggested for the gravimetric determination of thallium, the more recent volumetric methods are based upon the ability of the thallic ion, formed by the use of an oxidizing agent, to liberate iodine from potassium iodide (*108*, *111*, *237*).

TOXICOLOGIC PROPERTIES

Thallium compounds, which are extremely toxic to higher forms of life, do not precipitate proteins *in vitro*, according to Dixon (*86*). The salts are not markedly bactericidal (*223a*), but the metal in the presence of air is said to have a strong oligodynamic action upon certain bacteria (*41*).

Deaths have occurred among toads, mice, rats, rabbits, dogs, ducks, geese and quail as the result of the oral administration of one or another

soluble compound of thallium in amounts equivalent to from 6 to 40 mg. of the metal per kilogram of body weight (*32, 61, 112, 144, 157, 176, 196, 201, 204, 209, 247, 259, 263, 279*). For dogs, Gettler and Weiss (*112*) estimate the lethal dose as 12 to 15 mg. per kilogram, while Munch and Silver (*201*) give the following percentages of deaths occurring among rats given various doses of the sulfate:

Dose Milligrams/Kilogram	*Mortality percentage*
10	0
15	12
20	37
25	73
greater than 35	100

The available data indicate that results are not greatly different when the subcutaneous or intravenous route of administration is employed, but precise values cannot be given. Buschke and Peiser (*51*) found that organic compounds of trivalent thallium, such as thallium dimethyl bromide, are only one-tenth as toxic as thallous acetate when administered to mice. They assume from this that the organometallic radical does not break down in the body to yield the toxic thallous ion. Other investigators state that certain trivalent thallium compounds are among the most toxic compounds of that metal (*144*).

Marmé (*186*) as well as Swain and Bateman (*259*) offered some evidence that the action of the metal is cumulative. The latter investigators found that the effects of administering 200 mg. of a thallium compound to a dog in divided doses over a period of 13 days were as marked as those resulting from the giving of a similar amount within 4 days. Severe intoxication occurred in rats as a result of the oral administration of 0.2 mg. of the acetate per rat daily for several weeks (*47*). The statement that a tolerance for small amounts of the metal can be developed has been attributed to Marmé (*186*), whose paper is inaccessible. No other information in regard to this feature of the toxicity of thallium is available.

THE NATURE OF THE TOXICOLOGIC RESPONSE

The feature of the toxic response to thallium that has aroused the greatest interest—its ability to cause a loss of hair—was apparently discovered by Combemale (*62, 63*) in 1898. In accordance with the belief then that thallium was useful in treating colitis and in lessening the night sweats of phthisis, he instructed a patient to take a pill containing 0.1 gm. of a salt of thallium on each of 4 days. Several days later there was a complete and rapid loss of the hair, an observation that was soon confirmed by Huchard (*140*), Dubreuille (*93, 94*), Jeanselme (*146, 147*) and Guinard (*129*) on patients, and by others (*44*) on rabbits and guinea pigs. The onset of alopecia is always delayed for a week or more and it does not occur

in animals that die within a few days of the administration of a large dose. Hallopeau (*131*) found that guinea pigs died without any loss of hair within 48 hours after a cutaneous application of an ointment containing 50 percent of a thallium salt.

The signs of severe intoxication of animals by thallium—restlessness, tremors (*29*), ataxic gait, convulsive movements of the legs followed by partial paralysis, anorexia, loss of weight, constipation or bloody diarrhea, and dyspnea—are indicative of widespread damage to the nervous system and digestive tract and, to a lesser extent, the circulatory apparatus. At necropsy, lesions are encountered in the digestive tract, nervous system and kidneys.

Toads die in asphyxia following loss of control of their hind legs, after having been given doses of 1 to 30 mg. of thallium (*259*). In frogs, after a period during which there are convulsions, paralysis ensues, the respirations weaken and the heart stops in diastole (*75*, *157*). When a solution of a salt of thallium is perfused through the isolated heart of the frog, its contractions decrease in height and it finally stops in diastole (*40*). The action is diminished by the presence of calcium in the solution.

The appearance of signs of intoxication in mammals is usually delayed, rats dying from respiratory failure on the second or third day following the administration of a lethal dose (*19*). Cardiac depression has been mentioned by only a few investigators (*176*, *259*) and does not appear to be a usual feature of the response, although Mauro (*188*) found histologic changes in the myocardium. Curci (*75*) states that the blood pressure is increased. Dyspnea has been frequently observed, and several investigators have found bronchitis or broncho-pneumonia at necropsy.

Symptoms of nervous dysfunction are commonly encountered (*98*). Dogs become restless, and after a time exhibit an arching of the back and convulsive movements, especially of the hind legs, which later became partially paralyzed (*61*, *176*). Fishes swim in queer positions (*259*). In rabbits, an ataxic gait, tremors of the head, trismus and tonic-clonic convulsions and paralyses (*247*) have been described (*128*, *240*, *241*, *265*). Dixon (*86*) states that such signs are always delayed, the immediate action being limited to a relaxation of the smooth muscle of the bronchioles, intestine and uterus. He holds that the later signs result not so much from an action upon the medulla and spinal cord, as from a state of increased sensitivity of the autonomic system. A degree of faradic stimulation of the cervical sympathetic, insufficient to affect the pupil of a normal cat, caused strong mydriasis in a cat that had been given a small but unstated dose of a thallium compound. Dixon indicated, however, that the craniosacral nerves may be affected in a similar manner but to a lesser degree, and that the time required for a reflex to pass through the cord is lessened

by thallium, which he thought acted directly upon the neurones. Unfortunately, Dixon published only a brief discussion of this work, and made no allusion to the origin of the paralyses which are a late feature of the poisoning.

Histologic examinations by Greving and Gagel (*128*) showed changes typical of polyneuritis in the peripheral nerves, but no lesions in the vegetative nervous system. In the brain there were degenerative changes. in the Purkinje cells, the medial geniculate body and the nuclei of the oculomotor nerves. In the peripheral nerves and in certain tracts of the brain and cord of rats, Cortella (*65, 66, 67*) found the neurilemma thinned, swollen or ruptured at places, and noted varicose swellings of the axis cylinders. The ganglion cells were spherical in form, with their nuclei deformed and displaced toward the periphery. The cortical cells were pale, vacuolated and lacking in Nissl granules. The meninges were congested, the pia being thickened. Schneider (*240, 241, 242*), on the other hand, found that the brain was only slightly damaged. Ma and Mu (*179, 180*) found an almost complete absence of Nissl substance from the cells of the ganglia of the spinal cords of rats removed during the fourth week after the administration of a dose of the acetate equivalent to 8 mg. per kilogram of body weight.

Richet (*223*) and Rabuteau (*218*) noted that after the symptoms of nervous origin had been present for a time, there resulted an atrophy of the muscles, especially those of the jaw and spine. Muscular atrophy also has been described in human poisoning. Bacq suggested (*7*), from the results of experiments with the rectus abdominis of amphibia, that thallium, like the iodoacetates, may inhibit some enzymatic process concerned in muscular contraction.

Gastroenteric disturbances, including stomatitis, bloody diarrhea and loss of weight (*176, 247*), have been observed after the subcutaneous administration of thallium compounds. The repeated administration of small doses of thallium acetate to young rats caused an inhibition of growth (*47, 132*) and alterations of the bones (*44, 184, 185*), which were soft, curved, poorly calcified and had fusiform deposits of osteoid tissue. The marrow became fibrous, and Buschke and his co-workers (*31, 37, 48*) likened the in histologic appearance to that seen in ostetis fibrosa. Bony lesions appeared within 4 to 6 weeks in 68 percent of the rats given 0.2 mg. of thallium acetate daily (*50*), and were especially evident in the ribs and less so in the vertebrae and extremities.

Urabe (*271*) found thallium caused decreased amounts of ash in the teeth of rats and that small doses increased and large ones decreased the proportion of calcium in the ash. The content of phosphorus was not markedly affected. Rominger, Meyer and Bomskov (*227*) believe the retention of phosphorus is impaired in the first stage of intoxication, while

the calcium stores remain normal for a longer period, but decrease gradually as the poisoning advances. At one time Buschke and Peiser (*48*) asserted, without publishing the analyses, that the calcium content of the blood increases, but that the bones were unable to utilize it. Buschke (*44*) also asserted there may be hypochlorhydria and alkalosis.

A noninflammatory keratitis with progressive opacification of the cornea was observed by Richet (*223*). Several reports deal with the formation of cataracts in the eyes of chronically poisoned animals (*33*, *47*, *55*, *115*, *253*). No relation has been found between these and either the bony lesions or the degree of alopecia (*184*, *185*). Other lesions of the eye, as inflammations of the lids, intraocular hemorrhage, retrobulbar neuritis and partial atrophy of the optic nerve have been described (*43*.

In the forestomach of rats with chronic poisoning, inflammatory-proliferative lesions, including hyperkeratosis, papillomas and epithelial cysts and tufts extending into the muscularis mucosa have been described (*44*, *135*, *166*, *260*). They were limited to the areas lined by flat epithelial cells, and were not seen beyond the point of transition to the main stomach, nor on other organs covered with flat epithelium (*49*).

Polydipsia and polyuria have been noted by some investigators, while others state that in severe poisoning the damage to the kidney may be sufficient to cause complete anuria (*259*). In the kidney, Dal Collo (*77*, *78*) found parenchymal and vascular lesions, and Buschke, Loewenstein and Joel (*43*) mentioned changes in the cells of the tubules suggestive of those induced by chromium.

Hyperglycemia has been observed following the intravenous administration of a thallium salt (*156*), but in the development of chronic poisoning of rats transitory hyperglycemia is later followed by a decrease in the amount of sugar in the blood (*184*). Repeated subcutaneous injections of thallium compounds are said to increase the potassium and cholesterol of the blood and decrease the calcium (*155*, *156*). Testoni (*262*, *264*) failed to find hematoporphyrin in the urine of rabbits or dogs poisoned by thallium.

Buschke, in many papers asserted that endocrine disturbances of various types are common in chronic intoxication and may serve to explain many of the manifestations of the action of thallium. He noted that sexual activity was lessened (*139*), and observed apathy and somnolence in chronic poisoning (*46*), but Swain and Bateman (*259*) believed they had detected an aphrodisiac effect in an acutely poisoned dog. Various observers (*282*, *55*, *81*) have claimed that thallium inhibits the production of ovarian hormones in rats and less readily in mice. Doses so small as to induce no other effects were said to have produced this result, the cycle being resumed a few weeks after the regular feeding of thallium compounds had been stopped. Buschke and Bickel (*16*) asserted that even

during the continued administration of thallium, the cycle could be restored temporarily by the administration of ovarian or pituitary extracts. In contrast, Cox and Rodgerson (*68*) were unable to demonstrate any selective effect of thallium upon either the function or the histological appearance of the ovaries of rats. Buschke (*46*), however, stated that the testes may be completely atrophied and free from sperm. Baumann (*10*) and Mamoli (*184*) also reported some lesions in the sex glands.

Although it has been suggested that the convulsive response and the bony changes may be the result of interference with the action of the parathyroids, histologic examination of these glands by Mamoli (*184*) revealed few if any lesions. Lansbury (*164*), however, found the parathyroid gland markedly degenerated in the only rat he examined. The cells showed vacuolation and hyperchromatic, pyknotic and fragmented nuclear changes. Similar changes were observed in the pancreas, although the islands of Langerhans were but slightly affected.

Buschke and Peiser (*48*) asserted that thallium retards the growth and metamorphosis of tadpoles, and Mu and Hu (*194*) observed a transitory and slight diminution in the basal metabolic rate of rats 2 to 11 weeks following the subcutaneous administration of the acetate in doses of 8 to 12 mg. per kilogram of body weight. On the other hand, Julian Huxley and Curtis (*142*) were unable to demonstrate any antagonism between thallium and either iodine or thyroid extract upon the metamorphosis of tadpoles. They concluded that if thallium had any effect at all, it consisted in a very slight acceleration of the rate of metamorphosis. Balbi (*8*) also did not believe there is a specific action upon the thyroid. Histological changes in the thyroid were noted by Dal Collo (*77*, *78*) and by Mamoli (*184*), but were not seen by Baumann (*10*), Lansbury (*164*), or Buschke, Loewenstein and Joel (*43*). Ma and Mu (*179*, *180*) examined the thyroid of rats at various intervals following the subcutaneous administration of a dose of 8 mg. of the acetate per kilogram. During the first week, the Golgi apparatus in some of the thyroid cells changed from a network at the side of the nucleus into droplets, the mitochondria changed from filaments into segmented granules and the colloid assumed an acidophilic reaction. During the second week the droplets and granules of the Golgi apparatus and the mitochondria became much finer and were dispersed in the distal portion of the cells. By the third week the thyroid cells had become flattened, and their nuclei were poorly stained, while many vacuoles were present in the acidophilic colloid. Recovery then began and was complete in about 6 weeks.

It has been asserted by Buschke and Peiser (*46*) that the adrenals either became devoid of adrenaline or contained less than the normal amount. The lipoid of the adrenals and skin of rats was also said to be reversibly diminished in chronic thallium poisoning (*45*). The reticulo-endothelial

apparatus of the liver and the sinuses of the splenic veins were also swollen (*43*).

Contrary to the belief of Buschke (*35*) that the toxic response is the result of a functional deficiency on the part of the endocrines, the evidence indicates that in those instances in which some measure of dysfunction of any of the glands of internal secretion has been demonstrated, this has not exceeded that which might be found in any animal under the influence of a general cellular poison.

Alterations in the cellular composition of the blood of animals, detected after the administration of thallium, are neither characteristic nor regularly reproducible. Some observers believed that alterations similar to those due to lead could be produced (*158*). Seitz (*247*), however, found no stippled red cells after four injections of 0.2 c.c. of a 1 percent solution of the acetate into rabbits, but mentioned polychromasia and a definite increase of lymphocytes. Others have found only occasional erythropenia and leucocytosis (*184, 100, 166*).

Landauer (*163*) described experiments which suggest the progeny of chronically poisoned male animals are adversely affected. The chicks of hens fertilized by poisoned cocks had a significantly higher mortality within the first 3 weeks after hatching than did those fertilized by normal cocks.

THE EPILATING ACTION OF THALLIUM ON ANIMALS AND ITS MECHANISM

Thallium is unique among the metals in its ability to produce epilation. This phenomenon occurs but rarely in acute poisoning either of man or animals (*172, 145*), although other types of cutaneous dysfunction, as a scaly erythema, have occasionally been observed. Following the administration of smaller doses, diffuse depilation occurs after a period of several days to 2 weeks (*26, 30, 15, 85*). This is said to be brought about more readily in the rat than in the guinea pig (*266, 267*). In the instance of the former species, the peroral administration of 0.1 mg. of the acetate daily from the tenth week to the fifth month led to a state of alopecia which was complete except for the so-called sensory hairs (*52*). By continuing the administration at this rate, it has been possible to keep rats in a state of nearly complete hairlessness for a year. Mice, dogs, rabbits and apes also exhibit this response (*206*). The threshold dose for epilation is 14 to 30 mg. per kilogram in the rabbit (*61*) and 8 to 17 mg. per kilogram in sheep (*204*). Young rats lose their hair more readily than do older ones (*3, 4, 14, 274, 275*). Spitzer (*253*) believes coarse hairs are more readily lost than lanugo hairs.

There is disagreement as to the ability of locally applied thallium compounds to produce epilation. It is very difficult to test this experimentally, since it is well known that thallium compounds may be absorbed through the skin in lethal amounts (*201*), so that a positive response might well be

the result of changes in the hair-forming apparatus induced by way of the nerves or bloodstream rather than by direct local action. Truffi (*266, 267*) states that when applied locally in small quantity to a circumscribed area, depilation occurs only around the point of application. Although Buschke and Peiser (*46*) concur, Dixon (*86*) is of the opinion that depilation does not result when thallium compounds are rubbed into the skin, but that thallium applied in small but unstated amounts stimulates the growth of hair. He found a more rapid growth of hair on the skin of a shaved rabbit upon which a small amount of a thallium compound had been applied, than had occurred in the case of another that had been shaved only. This stimulant action of thallium upon the growth of hair (*64*) has even been made the basis for the treatment of alopecia areata (*1, 39*).

The hair of the young of chronically-poisoned rats begins to grow normally 8 days after birth, but stops after another 8 to 12 days (*46, 52*).

It cannot be said the mechanism by which thallium causes hair to be lost is known (*100*). Buschke, a dermatologist who published over 40 speculative papers that were meager in experimental details, held the action is mediated in some manner by alterations in the function of one or another of the ductless glands in turn acting upon the sympathetic nervous system. He based this in part upon his inability to detect local changes in the skin adequate to account for the loss of hair (*46, 52, 55, 35, 36, 16*). As already mentioned, there is little evidence that thallium has a specific and marked action upon any endocrine gland, and the administration of preparations derived from the ovary, testes, thyroid or parathyroid concurrently with a thallium compound fails to prevent the loss of hair (*8, 12, 101, 13, 276, 278*). A thymus perparation seemed to increase it (*12*). That the effect is exerted through the central nervous system is the view of Olmer and Tian (*207*) and Pöhlmann (*214*).

Evidence for the belief that the sympathetic system is involved is found in the demonstration of Buschke (*46, 52*) and others (*203, 214,*) that in the case of rats the baldness may be complete except for the so-called sensory hairs. The muscles of these hairs of the eyebrow and muzzle are said to be striated and innervated by cerebrospinal nerves whereas the body hairs have a sympathetic innervation. Chang (*57*), however, opposes the view that the action of thallium is exerted through the nerves, since he observed that the loss of hair continued at the same rate in fresh autotransplants of skin as in the normal areas, even though there had been insufficient time for the development of innervation to the transplants. Italian observers tend to the view that the action of the metal is directly upon the hair follicles. Fiocco (*103*) described histologic changes in the skin and hair follicles, as well as erythema, desquamation and secondary epithelial degeneration, in chronically-poisoned animals. Mamoli (*183*) described atrophy of the skin, subcutaneous tissue, sebaceous and sweat glands. Hyperplasia of the stratum corneum and atrophy of the

hair follicle and its inner root layer (*95*), and hypertrophy and hyperplasia of the thickened sebaceous glands, also have been described.

Buschke and Peiser (*52*), unable to confirm these observations, offered as evidence against local damage to the follicle as a cause of the alopecia, the fact that the loss of hair is never permanent. Truffi (*266, 267, 268*) maintains that there is an histologically demonstrable direct action upon the hair follicles. Dixon, (*86*) states the epidermis and sebaceous glands remain almost normal, but that in the dermis there is an increased density of fibrous tissue. In the hair follicles he found that the collection of epithelial cells was smaller than usual, although there were no abnormalities in the dividing cells. He attributed the interruption in the normal growth of hair to a failure in the process of transition from the large polygonal cells to the stratified cells that form the hair. Leigheb (*167*) also reported atrophy of the papillae and degeneration of the germinal cells of the bulb and root sheath, with a moderate degree of atrophy of the sweat and sebaceous glands. Others noted underdevelopment of the skin (*14*), and hyperkeratosis with microabscesses beneath the corneum (*266, 267, 268, 273*). Baumann (*10*), who observed a direct pynotic action on the nuclei of the cells of the hair follicles, testes, spleen and thymus, concluded that the metal produced a generalized karyolysis. It seems very probable that degenerative and inflammatory changes in the skin play an essential role in causing the alopecia (*192*). D'Avanco (*78a*) found that when locally applied, thallium lessens the ability of the skin of rabbits to reduce orthodinitrobenzene.

POISONING IN MAN

Munch (*197, 198*) in 1933–4, collected records of 778 cases of poisoning by thallium, of which 46 were fatal. Other cases have been reported subsequently (*136, 20, 154, 243, 202, 270*). Jordon (*149*) described a case which followed the eating of a sandwich left on a shelf in a photographic laboratory, where it had become contaminated with thallium sulfate.

Ginsburg and Nixon (*114, 200*) described an incident in which 11 Mexicans were poisoned in California as a result of eating tortillas made from a stolen store of thallium-treated barley intended for use in the experimental eradication of ground squirrels. Although three recovered, six died, and two remained psychotic. In a second and similar incident, 31 persons were exposed, of whom 22 exhibited symptoms and 6 died.

In man, the signs and symptoms are mainly referable to the nervous system, and the alimentary tract. When large quantities have been taken such symptoms become evident after about 12 to 14 hours. Symptoms indicative of damage to the digestive tract are the first to appear, disturbances of the nervous system often being delayed for 2 to 5 days. Typical of the many descriptions of cases (*22, 137, 127, 175, 54, 150, 219, 141, 207, 151, 136, 20, 154, 243, 202, 270, 173, 130, 2, 205, 272, 118, 189, 58, 260, 110, 149,106, 107, 221, 109, 6, 113, 222, 165, 229, 193, 251, 250*)

is one by Unsfeld (*270*) in which a 24-year old girl attempted suicide by taking a spoonful of Zelio grains. Among the symptoms noted were colic, loss of sleep, neuralgic pains in the legs, and depression. A nodular erythema appeared, and there was delirum for a time. The hair was lost and the patient became emaciated; after partial recovery an ataxic gait persisted for more than 3 months. There also was marked atrophy of the muscles of the legs. In a second but less severe case, there were violent pains in the abdomen and loins and great weakness for several days, and the hair was lost after 3 weeks.

Symptoms referable to the digestive tract include severe paroxysmal abdominal pain, vomiting, and in some but not all cases, diarrhea. Hemorrhage and desquamation of the gastric mucosa may occur. Stomatitis, sometimes ulcerative, is frequent, the gum line may become bluish (*216*) and there may be salivation, in some instances of an extreme degree.

Delirium, choreiform movement of the head and extremities, convulsions, and death from respiratory failure have occurred in severe poisoning. A marked preagonal rise in temperature has occurred in several of the fatal cases, possibly due to a lesion of the tuber cinereum. In those that survive after acute poisoning, and in the more chronic cases, a paresthesia of the hands and feet develops and progresses to a frank peripheral neuritis. The legs are involved more frequently than the arms. The cranial nerves are often affected, giving rise to ptosis, strabismus, facial palsy, mydriasis, and often retrobulbar neuritis and optic atrophy (*181*, *171*, *182*, *256*, *258*). Sometimes there is pain in the eyeball and transitory anisocoria. Some writers have likened the manifestations to those of an extrapyramidal, hepatolenticular syndrome, and others have thought it resembled the pseudosclerosis of Westphal-Strümpell. Peripheral neuritis, although a prominent feature of many of the cases of intoxication and one noted by the earliest observers (*277*), has been absent in a few undoubted cases of poisoning by thallium (*219*). In several cases, death has been preceded by the onset of pulmonary edema or bronchopneumonia, but in others it is believed to have resulted from a progressive impairment of the brain and vagus nerve (*192*).

The incidence of signs and symptoms attributable to an impairment of the heart has been variable. Mentioned in various cases have been sinus tachycardia (*127*), bradycardia, angina pectoris (*187*) and increased blood pressure. Alterations of the electrocardiographic pattern have been attributed to injury of the vagus (*230*, *192*).

Salivation occurs in some patients (*216*), but in others there is dryness of the mouth and a constant sensation of thirst. In addition to alopecia, the onset of which is always delayed, there may be cutaneous lesions, as a scaly erythema (*172*), various types of eruptions and keratinization of the epithelium, ecchymoses and petechia. Conjunctivitis may occur and blebs may form on the eyelids (*109*, *216*). Trophic disorders of the nails

may lead to the appearance of white strips, especially on the finger nails (*23*).

Cascio Rocco (*225*) and Flamm (*105*) have asserted that the calcium metabolism may be disturbed and hypochlorhydria or achlorhydria have been noted (*139, 227*). Testoni (*264*) found that although the urine was highly pigmented, it did not contain hematoporphyrin, but Moeschlin, Zollinger and Luthy (*192*) found uroporphyrin and suggested that thallium affects porphyrin metabolism. Albuminuria is usual.

In the acute cases in California there were no characteristic changes in the formed elements of the blood and no stippling of the erythrocytes (*200*), but Flamm (*105*) stated that 16 days after the administration of an epilating dose to children there was a 21.7 percent increase in the number of leucocytes, with a 39 percent increase in the lymphocytes and an 80 percent increase in the eosinophiles.

Necropsies on the fatal cases in California revealed hyperemia and punctate hemorrhages in the gastric and upper intestinal mucosa and a marked fatty infiltration of the cells of the liver, with a tendency to central necrosis. The adrenal was the only endocrine gland affected, there being marked hyperemia, with small medullary hemorrhages and areas of necrosis and nuclear degeneration. There were profound changes in the central nervous system. The cortical vessels were engorged, and various degrees of chromatolysis were seen in the neurones, especially those of the pyramidal tract, third nucleus, substantia nigra, and pyramidal cells of the globus pallidus. The vessels were distended and there were localized areas of edema. In a more chronic case, there was striking edema of the pia-arachnoid membrane.

In fatal cases Gettler and Weiss (*112*) found degenerative changes in the nerve cells, axones and myelin sheaths of nerves, basal ganglia and cerebellum, and degeneration of the optic nerve, along with fatty infiltration of the liver, degenerative changes in the renal glomeruli and convoluted tubules. In the more acute cases, they found no characteristic lesions, observing only congestion of the internal organs, and stomatitis and punctate hemorrhages along the digestive tract. In subacute cases there were also congested cerebral and meningeal vessels, hyperemia and parenchymatous degeneration of the kidneys, granular or fatty degeneration of the liver, fatty degeneration of the heart, and edema and congestion of the lungs. Arijewitsch (5) also made mention of central necrosis of the liver and damage to the renal glomeruli and tubules. Moeschlin, Zollinger and Lüthy (192) found degenerative changes in lymph glands, hair follicles and the mucous membrane of the stomach and intestines, as well as degenerative changes in the autonomic and peripheral nervous systems, but observed no characteristic changes in the endocrine glands.

Since 1901, Buschke (*27*) has maintained an interest in the oral administration of thallium compounds for the epilation of children prior to the

treatment of tinea. Relatively safe procedures for this purpose were described by Cicero in Mexico City (*59*, *60*), Peter (*212*), Gonzales (*120*, *121*, *122*, *123*) and Delgado (*82*). Its use was approved by Bedford (*11*) who had one failure and 2 partial failures in 21 cases, and observed mild toxic signs in only 3 of these. All who used it thought it essential that the dose be exactly 8 mg. per kilogram, less being ineffective and more being dangerous. Buschke (*34*) recommended that the drug and the child be weighed by two physicians and that the procedure be supervised by a third to avoid error. He administered the salt in tablet form only to fasting, healthy, well-nourished children who had not yet reached the age of puberty. Many others have described the mode of administration in detail (*104*, *170*, *177*, *210*, *213*, *281*, *79*, *92*, *80*, *84*, *246*, *42*, *102*, *208*, *236*). Although some authors have held (*105*, *139*) that the material is not toxic when administered to children before the age of puberty, Munch (*196*) states that when administered to children in the recommended dosage of 8 mg. per kilogram, it has caused harm, and that in some cases toxic symptoms have developed following the administration of half that dosage. Aramaki (*3*, *4*) finds the nitrate more suitable than the acetate.

Since Bullard (*24*) described a case of poisoning from the medicinal use of thallium, many others have been reported, 26 cases having been described by Levy (*169*), others by Huerre (*141*), Olmer and Tian (*207*), Neal, Appelbaum, Gaul and Masselink (*202*) and Karrenberg (*151*). Dowling (*89*, *90*, *91*) believes that it produces mild symptoms in 25 percent of the cases in which it is used. Pains in the limbs are noted about 10 days after the administration of thallium, and persist for 8 to 10 days. Some combine this treatment with the use of the X-ray, administering half an epilating dose of the latter and 4 mg. of thallium acetate per kilogram (*226*).

Many accidents have resulted from miscalculation of the dosage (*76*, *178*, *245*, *189*, *152*, *224*). In some instances the symptoms have simulated those of acute abdominal disease (*220*), and in others, encephalitis (*117*, *229*) or polyneuritis (*249*). In still others, there have been psychic manifestations and kidney involvement (*83*). Munch (*198*) believes that poisoning occurred in about 5.5 percent of the cases in which it has been used. Although he found records of 17 deaths following its use under what were considered improper clinical conditions, there have been at least 6 deaths as a result of the use of the substance in the recommended dosage of 8 mg. per kilogram. In all, he believes that more than 600 persons have been poisoned to some extent as a result of the medicinal use of thallium.

At one time Sabouraud (*235*, *231*, *232*, *233*, *234*) used an ointment containing not more than 1 percent of thallium acetate, applying each day an amount not more than equal to two kernels of wheat. Because of the occurrence of accidents, he turned to the use of X-rays instead, but stated, how-

ever, that when used with care, no harm resulted from the daily use of the ointment over a period of 18 months. Among others noting toxic symptoms from the external use of thallium for purposes of epilation are Giovannini (*116*), Criado (*69*), and Prieto (*217*). Tschernogubow (*269*) maintains that a dose of 3–4 mg. of the acetate per kilogram of body weight in ointment form may be safely applied upon the skin of children.

More than 51 cases of poisoning resulted from indiscriminate sale of an ointment known as Koremlu, which contained about 7 percent of thallium acetate (*280, 96, 171, 181, 25, 126, 238*).

About 12 cases of industrial poisoning, none of which was fatal, were recorded by Teleky (*261*) and Rube and Hendricks (*228*). These were confined to three of the nine factories in which thallium compounds were handled, but most of the workers engaged in producing the metal or its salts were affected. Six of those who became ill were handlers of pyrites, four were exposed to thallium-bearing dusts, and two worked with the salts. Fairhall (*99*) notes the possibility of exposure during the arcing of thallium compounds in spectrographic laboratories, but no intoxication is known to have occurred. A few accidents have occurred among workers employing thallium salts in the control of rodents. One arose during the cleaning of a container in which grain impregnated with thallium had been kept. The spreading of such grain for the eradication of prairie dogs has resulted in the poisoning of sheep.

The onset of industrial intoxication has been characterized by excitement and sleeplessness, which for a time excited no attention. After exposure for a few weeks or months, pain was noted in the joints of the lower limbs, accompanied by muscular cramps and weakness, with loss of the reflex of Achilles tendon. In some cases symptoms progressed to a polyneuritis. After a few months the hair fell out. Other symptoms were salivation, anorexia, vomiting, diarrhea and loss of weight, depression, fatigue, hysterical laughter, cyanosis, tachycardia, bradycardia (*217*) and less frequently albuminuria. In one case, a total central scotoma occurred about 4 months after the appearance of the first symptoms, and there were also lesions of the iris and crystalline lens. In another case, optic atrophy resulted. In his examinations of the blood of workmen exposed to thallium, Meyer (*191*) found a lymphocytosis, the lymphocytes constituting 40 to more than 58 percent of the leucocytes. In a few cases, 7 percent of the cells were eosinophiles. Erythropenia developed gradually and normoblasts were found, but a punctate basophilia of the erythrocytes has not been noted.

ABSORPTION, DISTRIBUTION AND EXCRETION OF THALLIUM

Thallium is readily absorbed through the skin and from the digestive tract. In experiments of Bonani and Marino (*21*), thallium sulfate was absorbed from the esophagus of rabbits and dogs. As early as 1890, J. Blake, a California physician, found by spectroscopic examination that

thallium appeared in the lungs within a few minutes after the intravenous injection of a thallium salt (*17*). It has also been shown, in the case of rabbits, that the element appears in the urine within 2 hours after the administration (orally presumably) of thallium sulfate (*148*). In the acute outbreak of intoxication in California, the metal persisted in the urine of patients for 3 weeks. The concentration in the urine of two persons who survived, was 2.39 mg. of thallium per liter. In chronic cases, 2 months elapsed before the metal dissappeared from the urine. Within 36 days, dogs excrete in their urine about 60 percent of the quantity administered in a single oral dose. Shaw (*248*) and Lansbury (*164*) estimated that rats given repeated sublethal doses, excrete daily about 0.4 mg. of the metal per kilogram of body weight. Other data on the excretion of the metal have been given by Devane (*84*) and by Dostrowsky (*88*). In the case of lactating rats given lethal doses, the milk contained thallium in amounts sufficient to delay or arrest the growth of hair, and to inhibit the growth and development of the young, but not to kill them (*28, 97*).

Shaw (*248*) found that 35 to 70 percent of the thallium administered orally to geese, in a dose of 20 mg. of the metal per kilogram of body weight, was retained in the tissues when, 15 days after the dose had been given, death occurred. The metal has been recovered from the kidney, liver, lungs, heart, spleen, intestines and bone of fatally poisoned men in concentrations ranging from 3 to 11 parts per million (*199*). Bence Jones (*148*) found the element in the liver, kidney and spleen, but not in the blood, of rabbits killed 21½ hours after the administration of the sulfate. In one man, 3.3 mg. of thallium per 100 gm. of liver, 1.6 mg. per 98 gm. of kidney, and 5 mg. per 100 gm. of urine were found (*107*). In rats that had ingested Zelio grains, Schee (*239*) found 40 to 60 mg. percent of the metal in the muscles, viscera and feces, but none in the brain, although in the case of poisoned hens, it was possible to detect the metal in the brain. Olmer and Tian (*207*) found thallium spectroscopically in the concentration of 1 part per 50 millions in the cerebrospinal fluid of a severely poisoned man; after removing the cells by centrifugation, the amount was reduced to one-tenth of its former value. The metal accumulates in small amounts in the skin and hair (*206*). In experimental observation on rabbits, relatively large amounts were found in the liver and kidney with lesser amounts in the lungs, heart and urine (*257*). The metal differs from lead in that it is not retained selectively in bone, thallium phosphate being 50 times as soluble as calcium phosphate (*112*). Gettler and Weiss (*112*) who tabulated analytical data on six dogs and one human case, found that per unit weight the kidney, pancreas, spleen and muscles contained more thallium than did the liver or other organs. Since the element does not occur in normal tissues, the demonstration of as little as 0.5 mg. per 100 gm. of tissue suggests intoxication by thallium,

the content ranging from 0.5 to 10.0 mg. per 100 gm. of tissue in subacute and fatal cases.

Luck (*174*) found that eleven rats died after eating the flesh of a hen poisoned by thallium, but Shaw (*248*), from his observations of the amounts retained in the tissues, concludes that there is little likelihood that the flesh of game birds that had access to thallium because of its use as a rodenticide, would cause secondary poisoning in man. Relatively large amounts may be absorbed into the fetuses of pregnant animals (*139*).

THERAPY OF POISONING BY THALLIUM

In two carefully studied cases, Moeschlin, Zollinger and Lüthy (*192*) found therapy ineffective. Morphine and its derivatives were of value in combating neuritic pain. Although thiamine has been suggested to lessen the severity of the peripheral neuritis, there is no evidence that there is any specific antagonism between the action of thiamine and that of thallium. Whether the latter plays the role of an antivitamin has not been investigated. Remedies promoting glomerular filtration, and other means of promoting the elimination of the metal, such as stomach lavage and the administration of saline purgatives, have been proposed. Pilocarpine hydrochloride in doses of 5 mg. has been employed in acute intoxication, preferably on the third to fourth days (*200, 168, 119, 149*). Heat, stimulants, dextrose and calcium salts are regarded as of value in the symptomatic treatment.

Because of the relative insolubility of the iodide of thallium, Munch, Ginsburg and Nixon (*200*) suggested that the intravenous administration of 0.3 to 1 gm. of sodium iodide, daily, might tend to fix the metal in the body in relatively insoluble form (*143*) and so lessen the acute symptoms of intoxication. They were of the opinion that the metal might be mobilized later by the cautious intravenous administration of from 0.3 to 1 gm. of sodium thiosulfate, a remedy that had been employed by others (*19, 195, 56*). They cautioned against the use of quantities that might liberate amounts sufficient to cause acute intoxication, and recommended determinations of the urinary output as a guide in choosing the correct dosage. On the other hand, Gettler and Weiss (*112*) doubt that sodium thiosulfate mobilizes thallium, and Buschke, Duchan and Joseph (*39*) do not recommend its use.

Periodic examinations of men engaged in work with thallium are advisable, and to avoid the possibility of the absorption of the metal through the skin in toxic amounts, special working clothes and gloves should be worn. Care should be taken to avoid the inhalation of dusts that may contain thallium.

The earlier literature on thallium has been listed by Doan (*87*), and reviews of the toxicity of this element have been given by Hartnack (*133, 134*), Kunkele (*159*), Steck (*254*), Ormerod (*208*), Lansbury (*164*), Mahoney (*181*), and Buschke and Peiser (*53*).

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